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TITLE
CONTROLLED RELEASE OXYCODONE COMPOSITIONS

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Sir:

Transmitted herewith for filing is the patent application of:

Inventor: Benjamin Oshlack, et al.

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

Enclosed are:

[ ] _____ sheet(s) of drawing

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CONTROLLED RELEASE OXYCODONE COMPOSITIONS

BACKGROUND OF THE INVENTION

The present invention relates to a solid, controlled release oral dosage form for use in the treatment of moderate to severe pain.

It has previously been known in the art that controlled release compositions of hydromorphone or salts thereof could be prepared in a suitable matrix. For example, U.S. Patent No. 4,990,341 (Goldie), also assigned to the assignee of the present invention, describes hydromorphone compositions wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C, is between 12.5 and 42.5% (by wt) hydromorphone released after 1 hour, between 25 and 55% (by wt) released after 2 hours, between 45 and 75% (by wt) released after 4 hours and between 55 and 85% (by wt) released after 6 hours.

For example, this patent teaches that controlled release hydromorphone compositions can be prepared by incorporating the drug into a controlled release matrix (e.g. hydrophobic polymers, digestible long chain hydrocarbons, polyalkylene glycols), or by incorporating the drug into a normal release matrix and utilizing a coating that controls the release of the drug (e.g. a film coating comprising a wax, shellac or zein, a water insoluble cellulose, a polymethacrylate). In a particularly preferred embodiment, film coated spheroids of hydromorphone and microcrystalline cellulose are film-coated to obtain the desired controlled release of the hydromorphone.

While controlled release compositions utilizing hydromorphone as the therapeutically active ingredient were obtained, controlled release compositions containing other therapeutically active agents having the same medicinal use

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(analgesia) and structurally related to hydromorphone, such as oxycodone, were not believed to be obtained when using similar techniques as those set forth in U.S Patent No. 4,990,341.

It has now been surprisingly discovered that controlled release compositions which include an analgesic other than hydromorphone are indeed obtainable via the methods set forth in U.S. Patent No. 4,990,341.

SUMMARY OF THE INVENTION

According to the present invention there is provided a solid, controlled release, oral dosage form, the dosage form comprising a therapeutically effective amount of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

Preferably, the dosage form contains an analgesically effective amount of oxycodone or a salt thereof. However, other related analgesically effective agents may also be used, including hydromorphone, dihydrocodeine, codeine, dihydromorphine, morphine, buprenorphine, salts thereof, and the like.

USP Paddle Method is the Paddle Method described, e.g., in U.S. Pharmacopoeia XXII (1990).

In the present specification, "independent of pH" means that the difference, at any given time, between the amount of oxycodone released at pH 1.6 and the amount released at any other pH up to, and including, pH 7.2 (when measured in vitro using the USP Paddle Method at 100 rpm in 900 ml aqueous buffer) is 10% (by weight) or less. The amounts released being, in all cases, a mean of at least three experiments.

DETAILED DESCRIPTION

In order to obtain a controlled release drug dosage form having at least a 12 hour therapeutic effect, it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4-8 hours after administration (in a single dose study). The present inventors have surprisingly found that, in the case of oxycodone, a peak plasma level at between 2-4 hours after administration gives at least 12 hours pain relief and, most surprisingly, that the pain relief obtained with such a formulation is greater than that achieved with formulations giving peak plasma levels (of oxycodone) in the normal period of 1-2 hours after administration.

Furthermore, in the case of the present dosage form, therapeutic levels are generally achieved without concurrent side effects, such as nausea, vomiting, constipation and drowsiness, which are often associated with high blood levels of oxycodone. There is also evidence to suggest that the use of the present dosage forms leads to a reduced risk of drug addiction.

A further advantage of the present composition, which releases oxycodone at a rate that is independent of pH between 1.6 and 7.2, is that it avoids dose dumping upon oral administration. In other words, the oxycodone is released evenly throughout the gastrointestinal tract.

The present oral dosage form may be presented as, for example, granules, spheroids or pellets in a capsule or in any other suitable solid form. Preferably, however, the oral dosage form is a tablet.

The present oral dosage form preferably contains between 1 and 50 mg, most especially between 10 and 30 mg, of oxycodone hydrochloride. Alternatively the dosage form may contain molar equivalent amounts of other oxycodone salts or of the oxycodone base.

The present matrix may be any matrix that affords in vitro dissolution rates of oxycodone within the narrow ranges required and that releases the oxycodone in a pH independent manner. Preferably the matrix is a controlled release matrix, although normal release matrices having a coating that controls the release of the drug may be used. Suitable materials for inclusion in a controlled release matrix are

(a) Hydrophilic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic polymer.

(b) Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids,

fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatc) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of at least one polyalkylene glycol.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol.

The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxycodone release required. Preferably however, the oral dosage form contains between 5% and 25%, especially between 6.25% and 15%, (by wt) of the at least one hydroxyalkyl cellulose.

The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of oxycodone release required. It will also depend on whether at least one

polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In a preferred embodiment, the controlled release composition comprises from about 5 to about 25% acrylic resin and from about 8 to about 40% by weight aliphatic alcohol by weight of the total dosage form. A particularly preferred acrylic resin comprises Eudragit™ RS PM commercially available from Rohm Pharma.

In the present preferred dosage form, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/ polyalkylene glycol determines, to a considerable extent, the release rate of the oxycodone from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1000 and 15000 especially between 1500 and 12000.

Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

As an alternative to a controlled release matrix, the present matrix may be a normal release matrix having a coat that controls the release of the drug. In particularly preferred embodiments of this aspect of the invention, the present dosage form comprises film coated spheroids containing active ingredient and a non-water soluble spheronising agent. The term spheroid is known in the pharmaceutical art and means a spherical granule having a diameter of between 0.5 mm and 2.5 mm especially between 0.5 mm and 2 mm.

The spheronising agent may be any pharmaceutically acceptable material that, together with the active ingredient, can be spheronised to form spheroids. Microcrystalline cellulose is preferred.

A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). According to a preferred aspect of the present invention, the film coated spheroids contain between 70% and 99% (by wt), especially between 80% and 95% (by wt), of the spheronising agent, especially microcrystalline cellulose.

In addition to the active ingredient and spheronising agent, the spheroids may also contain a binder. Suitable binders, such

as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

The spheroids are preferably film coated with a material that permits release of the oxycodone (or salt) at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other ingredients, the in-vitro release rate outlined above (between 12.5% and 42.5% (by wt) release after 1 hour, etc.).

The film coat will generally include a water insoluble material such as

(a) a wax, either alone or in admixture with a fatty alcohol,

(b) shellac or zein,

(c) a water insoluble cellulose, especially ethyl cellulose,

(d) a polymethacrylate, especially Eudragit®.

Preferably, the film coat comprises a mixture of the water insoluble material and a water soluble material. The ratio of water insoluble to water soluble material is determined by, amongst other factors, the release rate required and the solubility characteristics of the materials selected.

The water soluble material may be, for example, polyvinylpyrrolidone or, which is preferred, a water soluble cellulose, especially hydroxypropylmethyl cellulose.

Suitable combinations of water insoluble and water soluble materials for the film coat include shellac and polyvinylpyrrolidone or, which is preferred, ethyl cellulose and hydroxypropylmethyl cellulose.

In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, controlled release, oral dosage form according to the present invention comprising incorporating ~~hydromorphone~~ oxycodone or a salt thereof in a controlled release matrix. Incorporation in the matrix may be effected, for example, by

(a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and oxycodone or a oxycodone salt,

(b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12}-C_{36} aliphatic alcohol, and

(c) optionally, compressing and shaping the granules.

Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/oxycodone with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the oxycodone.

The present solid, controlled release, oral dosage form may also be prepared, in the form of film coated spheroids, by

(a) blending a mixture comprising oxycodone or a oxycodone salt and a non-water soluble spheronising agent,

(b) extruding the blended mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed, and

(d) coating the spheroids with a film coat.

The present solid, controlled release, oral dosage form and processes for its preparation will now be described by way of example only.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not meant to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Controlled Release Oxycodone HCl 30 mg Tablets - Aqueous Manufacture

The required quantities of oxycodone hydrochloride, spray-dried lactose, and Eudragit™ RS PM are transferred into an appropriate-size mixer, and mixed for approximately 5 minutes. While the powders are mixing, the mixture is granulated with enough water to produce a moist granular mass. The granules are then dried in a fluid bed dryer at 60°C, and then passed through an 8-mesh screen. Thereafter, the granules are redried and pushed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60-70°C, and while the granules are mixing, the melted stearyl alcohol is added. The warm granules are returned to the mixer.

The coated granules are removed from the mixer and allowed to cool. The granules are then passed through a 12-mesh screen. The granulate is then lubricated by mixing the required quantity of talc and magnesium stearate in a suitable blender. Tablets

are compressed to 375 mg in weight on a suitable tabletting machine. The formula for the tablets of Example 1 is set forth in Table 1 below:

TABLE 1
Formula of Oxycodone HCl 30-mg Tablets

Component	mg/Tablet	percent (by wt)
Oxycodone Hydrochloride	30.0	8
Lactose (spray-dried)	213.75	57
Eudragit® RS PM	45.0	12
Purified Water	q.s*	--
Stearyl Alcohol	75.0	20
Talc	7.5	2
Magnesium Stearate	3.75	1
Total:	375.0	100

*Used in manufacture and remains in final product as residual quantity only.

The tablets of Example 1 are then tested for dissolution via the USP Basket Method, 37°C, 100 RPM, first hour 700 ml gastric fluid at pH 1.2, then changed to 900 ml at 7.5. The results are set forth in Table 2 below:

TABLE 2
Dissolution of Oxycodone 30 mg Controlled Release Tablets

Time	% Oxycodone Dissolved
1	33.1
2	43.5
4	58.2
8	73.2
12	81.8
18	85.8
24	89.2

EXAMPLE 2

Controlled Oxycodone HCl 10 mg Release Tablets - Organic Manufacture

The required quantities of oxycodone hydrochloride and spray dried lactose are transferred into an appropriate sized mixer and mix for approximately 6 minutes. Approximately 40 percent of the required Eudragit® RS PM powder is dispersed in Ethanol. While the powders are mixing, the powders are granulated with the dispersion and the mixing continued until a moist granular mass is formed. Additional ethanol is added if needed to reach granulation end point. The granulation is transferred to a fluid bed dryer and dried at 30°C; and then passed through a 12-mesh screen. The remaining Eudragit® RS PM is dispersed in a solvent of 90 parts ethanol and 10 parts purified water; and sprayed onto the granules in the fluid bed granulator/dryer at 30°C. Next, the granulate is passed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60-70°C. The warm granules are returned to the mixer. While mixing, the melted stearyl alcohol is added. The coated granules are removed from the mixer and allowed to cool. Thereafter, they are passed through a 12-mesh screen.

Next, the granulate is lubricated by mixing the required quantities of talc and magnesium stearate in a suitable blender. The granulate is then compressed to 125 mg tablets on a suitable tabletting machine.

The formula for the tablets of Example 2 is set forth in Table 3 below:

Table 3
Formula of Oxycodone HCl 10 mg Controlled Release Tablets

Component	Mg/Tablet	Percent (by wt)
Oxycodone hydrochloride	10.00	8
Lactose (spray-dried)	71.25	57
Eudragit® RS PM	15.00	12
Ethanol	q.s.*	--
Purified Water	q.s.*	--
Stearyl Alcohol	25.00	20
Talc	2.50	2
Magnesium stearate	1.25	1
Total:	125.00 mg	100

*Used only in the manufacture and remains in final product as residual quantity only.

The tablets of Example 2 are then tested for dissolution via USP Basket Method at 37°C, 100 RPM, first hour 700ml simulated gastric (pH 1.2) then changed to 900ml at pH 7.5. The results are set forth in Table 4 below:

Table 4
Dissolution of Oxycodone 10 mg
Controlled Release Tablets

Hour	% Dissolved
1	35.9
2	47.7
4	58.5
8	67.7
12	74.5
18	76.9
24	81.2

EXAMPLE 3

Controlled Release Oxycodone 10mg Tablets (Aqueous Manufacture)

Eudragit® RS 30D and Triacetin® are combined while passing though a 60 mesh screen, and mixed under low shear for approximately 5 minutes or until a uniform dispersion is observed.

Next, suitable quantities of Oxycodone HCl, lactose, and povidone are placed into a fluid bed granulator/dryer (FBD) bowl, and the suspension sprayed onto the powder in the fluid bed. After spraying, the granulation is passed through a #12 screen if necessary to reduce lumps. The dry granulation is placed in a mixer.

In the meantime, the required amount of stearyl alcohol is melted at a temperature of approximately 70°C. The melted stearyl alcohol is incorporated into the granulation while mixing. The waxed granulation is transferred to a fluid bed granulator/dryer or trays and allowed to cool to room temperature or below. The cooled granulation is then passed through a #12 screen. Thereafter, the waxed granulation is placed in a mixer/blender and lubricated with the required amounts of talc and magnesium stearate for approximately 3 minutes, and then the granulate is compressed into 125 mg tablets on a suitable tabletting machine.

The formula for the tablets of Example 3 is set forth in Table 5 below:

Table 5
Formula of Controlled Release Oxycodone 10mg Tablets

Component	Mg/Tablet	percent (by wt)
Oxycodone Hydrochloride	10.0	8.0
Lactose (spray dried)	69.25	55.4
Povidone	5.0	4.0
Eudragit® RS 30D (solids)	10.0*	8.0
Triacetin®	2.0	1.6
Stearyl Alcohol	25.0	20.0
Talc	2.5	2.0
Magnesium Stearate	1.25	1.0
Total:	125.0	100.0

*Approximately 33.33 mg Eudragit® RS 30D Aqueous dispersion is equivalent to 10mg of Eudragit® RS 30D dry substance.

The tablets of Example 3 are then tested for dissolution via the USP Basket Method at 37°C, 100 RPM, first hour 700ml simulated gastric fluid at pH 1.2, then changed to 900ml at pH 7.5.

Table 6
Dissolution of Oxycodone 10mg
Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	38.0
2	47.5
4	62.0
8	79.8
12	91.1
18	94.9
24	98.7

EXAMPLES 4-5

In Example 4, 30 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 1.

In Example 5, 10 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 2.

Thereafter, dissolution studies of the tablets of Examples 4 and 5 are conducted at different pH levels, namely, pH 1.3, 4.56, 6.88 and 7.5.

The results are provided in Tables 7 and 8 below:

Table 7 - Example 4
Percentage Oxycodone HCl 30 mg Tablets
Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	29.5	43.7	61.8	78.9	91.0	97.0	97.1
4.56	34.4	49.1	66.4	82.0	95.6	99.4	101.1
6.88	33.8	47.1	64.4	81.9	92.8	100.5	105.0
7.5	27.0	38.6	53.5	70.0	81.8	89.7	96.6

Table 8 - Example 5
Percentage Oxycodone HCl - 10 mg Tablets
Dissolve Over Time

pH	1	2	4	8	12	18	24
1.3	25.9	41.5	58.5	73.5	85.3	90.7	94.2
4.56	37.8	44.2	59.4	78.6	88.2	91.2	93.7
6.88	34.7	45.2	60.0	75.5	81.4	90.3	93.9
7.5	33.2	40.1	51.5	66.3	75.2	81.7	86.8

EXAMPLES 6–11

In examples 6–11, 4 mg and 10 mg oxycodone Hcl tablets were prepared according to the formulations and methods set forth in the assignee's U.S. Pat. No. 4,844,909.

In Example 6, oxycodone hydrochloride (10.00 gm) was wet granulated with lactose monohydrate (417.5 gm) and hydroxyethyl cellulose (100.00 gm), and the granules were sieved through a 12 mesh screen. The granules were then dried in a fluid bed dryer at 50° C and sieved through a 16 mesh screen

Molten cetostearyl alcohol (300.0 gm) was added to the warmed oxycodone containing granules, and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Talc (15.0 gm) and magnesium stearate (7.5 gm) were then added and mixed with the granules. The granules were then compressed into tablets.

Example 7 is prepared in the same manner as Example 6; however, the formulation includes 10 mg oxycodone HCl/tablet. The formulas for Examples 6 and 7 are set forth in Tables 9 and 10, respectively.

Table 9
Formulation of Example 6

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Purified talc	6.0	15.0
Magnesium stearate	3.0	7.5

Table 10
Formulation of Example 7

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 8, 4 mg oxycodone HCl controlled release tablets are prepared according to the excipient formula cited in Example 2 of U.S. Patent No. 4,844,909. The method of manufacture is the same as set forth in Examples 6 and 7 above. Example 9 is prepared according to Example 8, except that 10 mg oxycodone HCl is included per tablet. The formulas for Examples 8 and 9 are set forth in Tables 11 and 12, respectively.

Table 11
Formulation of Example 8

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Anhydrous Lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

Table 12
Formulation of Example 9

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Hydrous lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 10, oxycodone 4 mg controlled release tablets are prepared with the same excipient formula cited in Example 3 of U.S. patent No. 4,844,909.

Oxycodone hydrochloride (32.0 gm) was wet granulated with lactose monohydrate (240.0 gm) hydroxyethyl cellulose (80.0 gm) and methacrylic acid copolymer (240.0 gm, Eudragit® L-100-55), and the granules were sieved through a 12 mesh screen. The granules were then dried in a Fluid Bed Dryer at 50° C and passed through a 16 mesh screen.

The warmed oxycodone containing granules was added molten cetostearyl alcohol (240.0 gm), and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen. The granules were then compressed into tablets.

Example 11 is prepared in identical fashion to Example 10, except that 10 mg oxycodone HCl is included per tablet. The

formulations for Examples 10 and 11 are set forth in Tables 13 and 14, respectively.

Table 13
Formulation of Example 10

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	32.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

Table 14
Formulation of Example 11

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	80.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

Next, dissolution studies were conducted on the tablets of Examples 6–11 using the USP basket method as described in the U.S. Pharmacopoeia XXII (1990). The speed was 100 rpm, the medium was simulated gastric fluid for the first hour followed by simulated intestinal fluid thereafter, at a temperature of 37° C. Results are given in Table 15.

TABLE 15
DISSOLUTION STUDIES OF EXAMPLES 6-11

Time (hrs)	% Oxycodone Dissolved Ex. 6	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11
1	23.3	25.5	28.1	29.3	31.3	40.9
2	35.6	37.5	41.5	43.2	44.9	55.6
4	52.9	56.4	61.2	63.6	62.1	74.2
8	75.3	79.2	83.7	88.0	82.0	93.9
12	90.7	94.5	95.2	100.0	91.4	100.0

EXAMPLES 12–16
Clinical Studies

In Examples 12–16, randomized crossover bioavailability studies were conducted employing the formulation of Examples 2 (organic manufacture) and 3 (aqueous manufacture).

In Example 12, a single dose fast/fed study was conducted on 24 subjects with oxycodone tablets prepared according to Example 3.

In Example 13, a steady-state study was conducted on 23 subjects after 12 hours with oxycodone tablets prepared according to Example 2, and compared to a 5 mg oxycodone immediate-release solution.

In Example 14, a single dose study was conducted on 8 subjects with 2 x 10mg oxycodone tablets prepared according to Examples 2 and 3, respectively, compared to a 20 mg oxycodone immediate release solution.

In Example 15, a single dose study was conducted on 22 subjects using oxycodone tablets prepared according to Example 3, and compared to a 20mg oxycodone immediate release solution.

In Example 16, a 12 subject single-dose study was conducted using 3 x 10mg oxycodone tablets prepared according to Example 3, and compared to a 30mg oxycodone immediate release solution.

The results of Examples 12–16 are set forth in Table 16.

Table 16

Example	Dosage	AUC ng/ml/hr	Cmax ng/ml	Tmax hr
12	10mg CR Fast	63	6.1	3.8
	10 mg CR Fed	68	7.1	3.6
13	5 mg IR q6h	121	17	1.2
	10 mg CR q12h	130	17	3.2
14	20mg IR	164	24	2.2
	2 x 10mg CR	117	14	3.1
	2 x 10mg CR	129	14	2.6
15	20mg IR	188	40	1.4
	2 x 10mg CR	197	18	2.6
16	30mg IR	306	53	1.2
	3 x 10mg CR	350	35	2.6
	30mg CR	352	36	2.9

IR denotes immediate-release oxycodone solution.
CR denotes controlled-release tablets

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A solid, controlled release, oral dosage form, the dosage form comprising an analgesically effective amount of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C is between 12.5% and 42.5% (by wt) ~~hydromorphone~~ oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

2. A dosage form according to claim 1 wherein the in vitro dissolution rate is between 17.5% and 38% (by wt) oxycodone released after 1 hour, between 30% and 50% (by wt) oxycodone released after 2 hours, between 50% and 70% (by wt) oxycodone released after 4 hours and between 60% and 80% (by wt) oxycodone released after 6 hours.

3. A dosage form according to claim 2 wherein the in vitro dissolution rate is between 17.5% and 32.5% (by wt) oxycodone released after 1 hour, between 35% and 45% (by wt) oxycodone released after 2 hours, between 55% and 65% (by wt) oxycodone released after 4 hours and between 65% and 75% (by wt) oxycodone released after 6 hours.

4. A dosage form according to claim 1 wherein the peak plasma level of oxycodone occurs between 2.25 and 3.75 hours after administration of the dosage form.

5. A dosage form according to claim 1 wherein a therapeutically effective amount of an oxycodone salt comprises between 2 and 50 mg of oxycodone hydrochloride.

6. A dosage form according to claim 1 wherein a therapeutically effective amount of an oxycodone salt comprises between 2 and 40 mg of oxycodone hydrochloride.

7. A solid controlled release oral dosage form, comprising an analgesically

(a) effective amount of oxycodone or a salt thereof;

(b) an effective amount of a controlled release matrix selected from the group consisting of hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from about 98 to about 50 carbon atoms, and polyalkylene glycols; and

(c) a suitable amount of a suitable pharmaceutical diluent, wherein said composition provides an in vitro dissolution rate of the dosage form when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C is between 12.5% and 42.5% (by wt) a oxycodone ~~hydromorphone~~ released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being

independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

8. The controlled release composition of claim 7, wherein said controlled release matrix comprises an acrylic resin.

9. The controlled release composition of claim 8 which contains from about 2 to about 50 mg of oxycodone hydrochloride.

10. A solid controlled release oral dosage form, comprising

(a) an analgesically effective amount of spheroids comprising oxycodone or a salt thereof and either a spheronising agent or an acrylic polymer or copolymer;

(b) a film coating which controls the release of the oxycodone or oxycodone salt at a controlled rate in an aqueous medium, wherein said composition provides an in vitro dissolution rate of the dosage form; and

(c) a suitable amount of a suitable pharmaceutical diluent, wherein said composition provides an in vitro dissolution rate of the dosage form when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C between 12.5% and 42.5% (by wt) oxycodone ~~hydromorphone~~ released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the

peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

11. The controlled release composition of claim 10, wherein said film coating comprises a water insoluble material selected from the group consisting of shellac or zein, a water insoluble cellulose, or a polymethacrylate.

12. The controlled release composition of claim 11, which contains from about 2 to about 50 mg of oxycodone hydrochloride.

13. A controlled release tablet for oral administration comprising an analgesically effective amount of oxycodone or an oxycodone salt dispersed in a controlled release matrix, comprising

from about 5% to about 25% of an acrylic resin and from about 8% to about 40% of at least one aliphatic alcohol of 12-36 carbon atoms, by weight, wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C is between 12.5% and 42.5% (by wt) ~~hydromorphone~~ oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

14. A process for the preparation of a solid, controlled release, oral dosage form comprising

incorporating an analgesically effective amount of oxycodone or a salt thereof in a controlled release matrix comprising from about 5% to about 25% of an acrylic resin and from about 8% to about 40% of at least one aliphatic alcohol of 12-36 carbon atoms, by weight,

wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method of 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 25% and 60% (by weight) oxycodone release after 1 hour, between 45% and 80% (by weight) oxycodone released after 2 hours, between 60% and 90% (by weight) oxycodone released after 3 hours, and between 70% and 100% (by weight) oxycodone released after 4 hours, the in vitro release rate being independent of pH between 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

15. The process of claim 14, further comprising

wet granulating said oxycodone or a salt thereof with said acrylic resin in alcohol to form a granulate thereof;

adding said at least one aliphatic alcohol in a substantially liquid state to said granulate to obtain coated granules; and

compressing and shaping the granules.

16. The process of claim 14, further comprising

wet granulating said oxycodone or a salt thereof with said acrylic resin in water to form a granulate thereof;

adding said at least one aliphatic alcohol in a substantially liquid state to said granulate to obtain coated granules; and

compressing and shaping the granules.

17. The process of claim 16, wherein a portion of said acrylic resin is dispersed in a suitable solvent and sprayed onto said granulate prior to adding said at least one aliphatic alcohol.

800,579

ABSTRACT OF THE DISCLOSURE

A solid controlled release, oral dosage form, the dosage form comprising a therapeutically effective amount of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method of 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C is between 12.5% and 42.5% (by weight) oxycodone released after 1 hour, between 25% and 55% (by weight) oxycodone released after 2 hours, between 45% and 75% (by weight) oxycodone released after 4 hours and between 55% and 85% (by weight) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

91-318

U.S.A.
DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CONTROLLED RELEASE OXYCODONE COMPOSITIONS

the specification of which (check one) ☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).
I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)			Priority claimed	
(Number)	(Country)	(Day/Month/Year filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occured between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing date)	(Status) (patented, pending, abandoned)

And I hereby appoint Harold D. Steinberg, Registration No. 17,255, Martin G. Raskin, Registration No. 25,642, and Clifford M. Davidson, Registration No. 32,728 my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith; correspondence address: STEINBERG & RASKIN, 1140 Avenue of the Americas, New York, N.Y. 10036; Telephone: 212-768-3800; Fax: 212-382-2124
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Benjamin OSHLACK
Inventor's signature: Benjamin Oshlack
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Second Inventor's signature: Mark Chasin
Date: November 26, 1991
Residence: Manalpan, New Jersey 07726 NJ
Citizenship: U.S.A.
Post Office Address: 3 Wayne Court, Manalpan, New Jersey 07726

Full name of joint Inventor, if any: John Joseph MINOGUE
Third Inventor's signature: John Joseph Minogue
Date: November 26, 1991
Residence: Mount Vernon, New York 10552 NY
Citizenship: U.S.A.
Post Office Address: 33 East Grand Street, B-2B, Mount Vernon, New York 10552

Full name of joint Inventor, if any: _____
Fourth Inventor's signature: _____
Date: _____
Residence: _____
Citizenship: _____
Post Office Address: _____

Full name of joint Inventor, if any: _____
Fifth Inventor's signature: _____
Date: _____
Residence: _____
Citizenship: _____
Post Office Address: _____

Full name of joint Inventor, if any: _____
Sixth Inventor's signature: _____
Date: _____
Residence: _____
Citizenship: _____
Post Office Address: _____

wm.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/800,549	11/27/91	OSHLACK	B 91-318

EXAMINER
SPEAR, J

ART UNIT	PAPER NUMBER
1502	2

DATE MAILED: 04/30/92

STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 11-27-1991 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ ~~days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

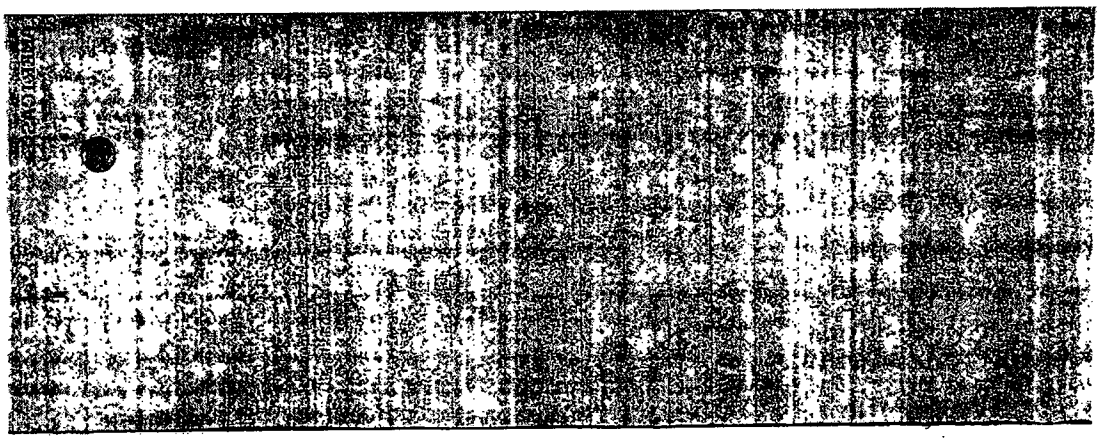
1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-17 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

98

EXAMINER'S ACTION



The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (e), (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Goldie et al. U.S. 4,990,341 in view of Oshlack et al. U.S. 4,861,598.

Goldie et al. teaches a controlled release oral dosage form of an analgesic, hydromorphone, wherein the active drug is in a controlled release matrix. See column 3. Goldie further teaches peak plasma levels attained between 2.25 and 3.75 hours (see claim 4). The reference further teaches dosage ranges which are the same or substantially the same as those claimed. Conventional matrix forming materials are disclosed in columns 3 and 4. Coating materials are shown at col. 4, lines 37-45. Conventional granulation processes are disclosed in the Examples. Although Goldie does not use oxycodone, both oxycodone and hydromorphone being

derivatives of natural alkaloids with many structural similarities are considered interchangeable in the matrix compositions.

Oshlack is relied on for teaching matrix compositions as those of applicants wherein the active agent is oxycodone. See Example II. Claim 1.

It would have been obvious to one of ordinary skill in the art to use oxycodone in the Goldie et al. invention. The motivation to do so is suggested by a desirability to provide optimum drug bioavailability by controlled release from a matrix composition.

Claims 1-17 are rejected.

Any inquiry concerning this communication should be directed to James M. Spear at telephone number (703) 308-2351.

J. Spear/mbb
April 27, 1992

DOUGLAS W. ROBERTS
SUPERVISORY PATENT EXAMINER
ART UNIT 152

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP--APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	800549	1502	2
	APPLICANT(S) OSHLACK et al.		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	4861598	8-89	Oshlack	424	470	/
	B	4990341	2-91	Goldie et al.	424	484	4-89
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R	
S	
T	
U	

EXAMINER	DATE
James M. Spear	4-18-92

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

840:P3-117

15 SP3 11/18/92

MAIL ROOM OCT 15 28 1992 PAT. & TRADEMARK OFF.

91-318

UNITED STATES PATENT AND TRADEMARK OFFICE

J. Spear Art Unit: 1502

Re: Application of: Benjamin OSHLACK, et al.

Serial No.: 07/800,549

RECEIVED NOV 10 1992 GROUP 1500

Filed: November 27, 1991

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

PETITION FOR EXTENSION UNDER 37 CFR 1.136(a)

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

October 22, 1992

Sir:

Applicants petition the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated April 30, 1992 for three months from July 30, 1992 to October 30, 1992.

Submitted herewith is a check for $840.00 to cover the cost of the extension.

Any deficiency or overpayment should be charged or credited to Deposit Account No. 19-4210. A duplicate copy of this sheet is enclosed.

Respectfully Submitted,
STEINBERG AND RASKIN

By: _____
Clifford M. Davidson
Reg. No. 32,728

Steinberg & Raskin
1140 Avenue of the Americas
New York, N.Y. 10036
(212) 768-3800

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Commissioner of Patents and Trademarks Washington, D.C. 20231" on October 22, 1992

STEINBERG & RASKIN

BY: _____

070 AA 11/07/92 07800549 1 117 840.00 CK

#4
11/18/92

91-318

MAIL ROOM OCT 28 1992 PAT & TRADEMARK OFF.

UNITED STATES PATENT AND TRADEMARK OFFICE

J. Spear

Re: Application of:

Serial No.:

Art Unit: 1502

Benjamin OSHLACK, et al.

07/800,549

RECEIVED
NOV 10 1992
GROUP 1500

Filed: November 27, 1991

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

RESPONSE

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

October 22, 1992

Sir:

In the Office Action dated April 30, 1992, the Examiner rejected claims 1-17 of the above-identified application under 35 U.S.C. §103 as being unpatentable over Goldie et al. (U.S. 4,990,341) in view of Oshlack (U.S. 4,861,598). In making this rejection, the Examiner relied upon Goldie as teaching a controlled release oral dosage form of hydromorphone, wherein the active ingredient is in a controlled release matrix, wherein peak plasma levels are attained between 2.25 and 3.75 hours. The Examiner further stated that this reference discloses conventional matrix forming materials, coating materials, and conventional granulation processes. Finally, the Examiner stated that the Goldie reference teaches "dosage ranges which are the same as those of applicants."

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Commissioner of Patents and Trademarks Washington, D.C. 20231" on October 22, 1992

STEINBERG & RASKIN

BY:

The Examiner concluded that "[a]lthough Goldie does not use oxycodone, both oxycodone and hydromorphone being derivatives of natural alkaloids with many structural similarities are considered interchangeable in the matrix compositions."

The Examiner cited Oshlack as teaching matrix compositions as those of applicants' wherein the active agent is oxycodone. The Examiner concluded that it "would have been obvious to one of ordinary skill in the art to use oxycodone in the Goldie et al. invention. The motivation to do so is suggested by a desirability to provide optimum drug bioavailability by controlled release from a matrix composition."

Applicants respectfully traverse the rejection on the merits for the following reasons.

1. **Controlled Release Opioid Analgesics Have a Wide Range of Appropriate Dosages to Manage Pain**

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients. This extraordinary wide range in the appropriate dosage makes the titration process particularly time consuming and resource consuming, as well as leaving the patient without acceptable pain control for an unacceptably long duration.

In the management of pain with opioid analgesics, it has been commonly observed and reported that there is considerable inter-individual variation in the response to a given dose of a given drug, and, therefore, considerable variability among patients in the dosage of opioid analgesic required to control pain without unacceptable side effects. This necessitates considerable effort on the part of clinicians in establishing the appropriate dose in an individual patient through the time consuming process of titration, which requires careful assessment

of both therapeutic and side effects and dosage adjustments over a period of days and sometimes longer before the appropriate dosage is determined.[1]

An opioid analgesic treatment which acceptably controls pain over a substantially narrower daily dosage range would, therefore, substantially improve the efficiency and quality of pain management.

2. **The Oxycodone Formulations of the Present Invention Provide Surprisingly Improved Results**

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours - around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general.

Morphine, which is considered to be the prototypic opioid analgesic, has also been formulated into a 12 hour controlled-release formulations (i.e., MS Contin®, commercially available from The Purdue Frederick Company). Despite the fact that both controlled-release oxycodone and controlled release morphine administered every 12 hours around-the-clock possess qualitatively comparable clinical pharmacokinetic characteristics, the oxycodone formulations of the presently claimed invention can be used over approximately 1/2 the dosage range as compared to seemingly similar controlled release

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[1] The American Pain Society's 3rd Edition of Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain explains that one should "be aware that the optimal analgesic dose varies widely among patients. Studies have shown that in all age groups, there is enormous variability in doses of opioids required to provide relief, even among opioid naive patients with identical surgical lesions...."

morphine formulations to control 90% of patients with significant pain.

A review of dose-response studies and relative analgesic assays of mu-agonist opioid analgesics, which include oxycodone, morphine, hydromorphone, levorphanol, methadone, meperidine, heroin, all indicate no significant deviation from parallelism in their dose response relationships. This is so well established that it has become an underlining principal providing for establishing relative analgesic potency factors and dose ratios which are commonly utilized when converting patients from one mu-agonist analgesic to another regardless of the dosage of the former. Unless the dose response curves are parallel, conversion factors would not be valid across the wide range of dosages involved when substituting one drug for another.

3. **The Present Invention Provides Important Clinical Advantages**

The clinical significance provided by the controlled release oxycodone formulations of the present invention at a dosage range from about 10 to about 40 mg every 12 hours for acceptable pain management in approximately 90% of patients with moderate to severe pain as compared to other opioid analgesics, requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing. The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

4. **The Results Obtained by the Present Invention are Not Obvious From the Prior Art**

It is respectfully submitted that one skilled in the art having knowledge of the controlled release oxycodone formulations of Goldie, et al. would not be motivated to prepare controlled release oxycodone formulations in a dosage range from about 10 mg to about 40 mg, which formulations thereby acceptably control pain over a substantially narrower, approximately four-fold range in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients utilizing controlled release hydromorphone, or controlled release opioid analgesics in general. One skilled in the art would certainly not arrive at this surprising result without the benefit of hindsight.

In view of the arguments presented, it is respectfully submitted that the Examiner's rejection on the merits has been overcome and should be removed.

An early and favorable action on the merits is earnestly solicited.

Respectfully Submitted,

Steinberg and Raskin

By: _____
Clifford M. Davidson
Reg. No. 32,728

STEINBERG AND RASKIN
1140 AVENUE OF THE AMERICAS
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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/800,549	11/27/91	OSHLACK	B 91-318

EXAMINER
SPEAR, J

STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

ART UNIT	PAPER NUMBER
1502	5

DATE MAILED: 02/03/93

This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-17 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

This action is in response to the amendment filed October 28, 1992, by Clifford M. Davidson.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention.

Claims 1, 7, 10 and 13 recite inconsistent terminology by claiming an oxycodone tablet and further reciting hydromorphone in the dissolution rate. Note the release after one hour for each claim.

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the

time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 14-17 remain rejected under 35 U.S.C. § 103 as being unpatentable over Goldie et al., U.S. 4,990,341 in view of Oshlack, U.S. 4,861,598.

The claims remain rejected for the reasons set forth in the prior office action, Paper No. 2, mailed 4/30/92.

In order to provide a complete and proper response it is deemed necessary that the objection to the disclosure be addressed prior to the next office action.

Any inquiry concerning this communication should be directed to James M. Spear at telephone number (703) 308-2351.

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
ART UNIT 152

Spear:amw
January 28, 1993

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/800549	11/27/91	Oshlack, Benjamin	91-318

EXAMINER	
Spear, J. M.	
ART UNIT	PAPER NUMBER
1502	6

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) James M. Spear (3) _____

(2) Harold D. Steinberg (4) _____

Date of interview 2-25-93

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No. If yes, brief description: _____

Agreement ☐ was reached with respect to some or all of the claims in question. ☐ was not reached.

Claims discussed: 1-17

Identification of prior art discussed: Goldie et al, Oshlack

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Discussed nature of dissolution rate with regard to prior art. Applicant will submit proposed declaration supporting unobviousness and unexpected results. Terminal disclaimer will be filed. Favorable consideration will be given for the Proposals discussed regarding allowability.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1–7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

☐ Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.

James M. Spear
Examiner's Signature

MAIL ROOM MAR 12 1993 PATENT & TRADEMARK OFFICE

91-318

7/C
4/15/93

UNITED STATES PATENT AND TRADEMARK OFFICE
J. Spear Art Unit: 1502

Re: Application of Benjamin OSHLACK, et al.
Serial No. 07/800,549
Filed: November 27, 1991
For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

RECEIVED
APR 0 8 1993
GROUP 150

AMENDMENT

Hon. Commissioner of Patents and Trademarks March 10, 1993
Washington D.C. 20231

Sir:

Responsive to the Office Action of February 3, 1993, please amend as follows:

IN THE CLAIMS:

Claim 1, line 6, change "hydromorphone" to --oxycodone--.

Claim 7, line 14, change "hydromorphone" to --oxycodone--.

Claim 10, line 13, change "hydromorphone" to --oxycodone--.

Claim 13, line 10, change "hydromorphone" to --oxycodone--.

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Commissioner of Patents and Trademarks, Washington, DC 20231" on March 10, 1993

STEINBERG & RASKIN

By: _____

REMARKS

The courtesy extended by Examiner Spear at the recent conference with the undersigned is most appreciated.

Applicants also wish to express appreciation to the Examiner for calling attention the typographical error in the claims wherein "hydromorphone" was inadvertently used instead of "oxycodone". This typographical error has been corrected by the instant Amendment.

At the conference, extensive discussion was had concerning the patentability of the present invention over the cited art, namely the Goldie, et al, and Oshlack patents.

As was pointed out to the Examiner at the conference, it is totally impossible to predict what dissolution rates for any particular drug will give rise to an extended duration of action, e.g. a 12 hour duration of action as set forth in this case. Even in the case of closely related drugs, predictability is impossible, and consequently, Applicants' discovery herein that oxycodone in a matrix having the dissolution in vivo and the other characteristics set forth in the claims of this case would provide 12 hours of relief when administered orally, clearly constitutes a patentable invention. This could not be predicted based upon the teaching of Goldie, et al., and furthermore, the teaching of Oshlack does not when combined with Goldie suggest the present invention.

This is all confirmed by the herewith submitted declaration of Dr. Robert F. Kaiko, a person truly skilled in this art, who not only sets forth that in his opinion one skilled in the art would not be able to accurately predict whether an oxycodone formulation such as that taught herein would provide the pharmacokinetics and pharmacodynamics set forth in the present claims, but Dr. Kaiko gives reasons why this could not be

predicted.

At the conference, Examiner Spear indicated that it seemed that the Applicants herein were nevertheless trying to claim the same invention as that set forth in the cited Goldie, et al. patent. In order to avoid this possibility, a Terminal Disclaimer is submitted herewith, along with the appropriate fee, disclaiming the terminal portion of any patent to be issued in this case beyond the expiration date of the Goldie, et al. patent.

In view of the submission herewith of the Declaration of Dr. Kaiko and of the Terminal Disclaimer, it is believed that Applicants have established the allowability of all of the claims in this case as presently set forth.

Accordingly, early action on the merits and allowance of the claims are respectfully solicited.

Respectfully submitted,

STEINBERG & RASKIN

Harold D. Steinberg

(212) 768-3800

HDS/aew
disk #8